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10/589,495	08/15/2006	Kenji Miyazaki	Q96529	8261

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EXAMINER	
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1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,495	MIYAZAKI ET AL.	
	Examiner	Art Unit	
	ROBERT XU	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/15/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Preliminary amendment filed on August 15, 2006, is acknowledged. Claims 1-23 are pending and have been fully considered.

Claim Objections

2. Claim 5 is objected to because of the following informalities: in the last step it recites "my" instead of "by". Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method comprising using a dipolar aprotic solvent, does not reasonably provide enablement for the method comprising obtaining the C-terminal-deleted peptide retained in a gel, as recited in claim 14, or for processing the sample in the gel, as recited in claims 15-16, under any other reaction conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. As specifically indicated in the specification, in order to obtain C-terminal-deleted peptides and retain them in the gel, as recited in claims 14-16, the reaction of cleavage using alkanoic anhydride should be performed in the dipolar aprotic solvent (page 41 lines 19-23). Otherwise, performing the reaction under anhydrous conditions will require dehydration of the gel with e.g. acetonitrile, which causes the gel to shrink.

Using dipolar aprotic solvent overcomes the gel-shrinking problem and keep the gel swollen, as disclosed in the specification (page 41 and last paragraph, page 42 and 1st - 3rd paragraph). It would have been an undue experimentation for a routineer in the art to search for other conditions of obtaining C-terminal-deleted peptides while retaining them in the gel, as recited in claims 14-16.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the limitation "the gel", which lacks antecedent basis, as no "gel" is recited in the parent claims.

Claim 15-16 recite the limitation "the processings", which lacks antecedent basis, since no "processings" were recited in the parent claims. Parent claims 1 and 5 recite only the step of obtaining C-terminal-deleted peptides. It is not clear, if this is what is meant by the limitation "the processings" recited in claim 15 and 16, which renders the language of claims 15 and 16 unclear and indefinite. Furthermore, if "the processings" means "obtaining C-terminal-deleted peptides", it is not clear from the parent claims, as to how the peptides are obtained while being retained in the gel. Are they obtained by performing a reaction of cleavage while being retained in a gel? If this is the case, this should be directly recited in the claim in order to make the claims clear and definite.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. **Claims 1-4, 22 and 23** are rejected under 35 U.S.C. 102(b) as being anticipated by Tsugita et al. (Electrophoresis, 1998) (Tsugita).

In regard to Claims 1, Tsugita teaches a method of analyzing the C-terminal amino acid sequence of the peptide. The method comprises:

obtaining C-terminal-deleted peptides lacking amino acid residues from the C-terminal by degrading the amino acid from the peptide C-terminal sequentially (see page 930, right col. 3rd paragraph);

measuring the molecular weight of the C-terminal-deleted peptides (see page 931, left col. 2nd paragraph); and

determining the decrease in molecular weight associated with the sequential degradation to identify the C-terminal sequence (see Table 3),

wherein the C-terminal amino acids are degraded by making the peptide in contact with an alkanoic anhydride (acetic anhydride) and pentafluoropropionic methyl ester (PFPMe) (see page 930, right col. 3rd paragraph).

In regard to Claim 2, Tsugita teaches measuring molecular weight of the C-terminal-deleted peptides and determining the peptide sequence from the difference between the molecular weight of the C-terminal-deleted peptides (see page 931, left col. 2nd paragraph; Table 3).

In regard to Claims 3 and 4, Tsugita teaches allowing a water solution containing N,N'-dimethylamino ethanol (DMAE) to act on the C-terminal-deleted peptide after obtaining the C-terminal-deleted peptide and before measuring the molecular weight of the C-terminal-deleted peptide (see page 930, right col. last 5 lines).

In regard to Claims 22 and 23, Tsugita teaches that the alkanoic anhydride is acetic anhydride (see page 930, right col. 3rd paragraph).

Claim Rejections - 35 USC § 102/103

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. **Claims 1-10, 12-16, 18-19, and 22-23** are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Miyazaki et al. (Seikagaku, 2003, IDS) (Miyazaki).

In regard to Claims 1, Miyazaki teaches a method of analyzing the C-terminal amino acid sequence of the peptide. The method comprises:

obtaining C-terminal-deleted peptides lacking amino acid residues from the C-terminal by degrading the amino acid from the peptide C-terminal sequentially (see abstract); wherein the C-terminal amino acids are degraded by making the peptide in contact with an alkanoic anhydride (acetic anhydride) (see abstract);

measuring the molecular weight of the C-terminal-deleted peptides (see page abstract).

Miyazaki does not literally teach determining the decrease in molecular weight associated with the sequential degradation to identify the C-terminal sequence. However, once the molecular weights of all the C-terminal-deleted peptides are measured, calculating the molecular weight difference between the molecular weight of the C-terminal-deleted peptides to derive the deleted amino acid is an inherent part of the method. At least it is obvious to ordinary skill in the art to calculate the molecular weight difference to derive the deleted amino acid.

In regard to Claim 2, Miyazaki teaches measuring molecular weight of the C-terminal-deleted peptides and determining the peptide sequence from the difference between the molecular weight of the C-terminal-deleted peptides (see abstract).

In regard to Claims 3 and 4, Miyazaki teaches allowing a water solution containing N,N'-dimethylamino ethanol (DMAE) to act on the C-terminal-deleted peptide

after obtaining the C-terminal-deleted peptide and before measuring the molecular weight of the C-terminal-deleted peptide (see abstract).

In regard to Claim 5, the first three steps of the claim are disclosed by Miyazaki as depicted in paragraph 9. Miyazaki also teaches cleaving C-terminal-deleted peptide at predetermined position by trypsin and measuring the molecular weight of C-terminal-deleted peptide-derived peptide fragments (see abstract). Determining the decrease in molecular weight associated with the sequential degradation from the difference between the molecular weight obtained in measuring the molecular weight of C-terminal-deleted peptide-derived fragments is an inherent part of Miyazaki's method or is obvious to ordinary skill in the art.

In regard to Claim 6, Miyazaki teaches obtaining peptide-derived peptide fragments by cleaving peptide with trypsin at predetermined positions (see abstract); and measuring the molecular weight of peptide-derived-peptide fragments, and C-terminal-deleted peptide-derived peptide fragments to determine the decrease in molecular weight of associated sequential degradation (see abstract).

In regard to Claim 7, Miyazaki uses acetic anhydride to acetylate N-terminus amino group and to form oxazolone at the C-terminal carboxyl group (see abstract). It is known in the art that the amino group of lysine is susceptible to acetylation and acetic anhydride acetylates amino group of lysine (N-acylation) and hydroxyl group of serine and threonine (O-acylation). Acetylated residues are protected from the cleavage of trypsin.

In regard to Claims 8 and 9, Miyazaki teaches treating C-terminal-deleted peptide with trypsin. The acetylated N-terminus amino group is protected from trypsin cleavage (see abstract).

In regard to Claim 10, the hydrolysis as taught by Miyazaki would remove acetyl group from O-acylation and therefore, would deprotect the side chain of serine and threonine from trypsin. The timing of the hydrolysis in the Miyazaki's method is after obtaining the C-terminal-deleted peptide and before obtaining the C-terminal-deleted peptide-derived peptide fragments (see abstract).

In regard to Claims 12 and 13, Miyazaki teaches allowing a water solution containing DMAE to act on the C-terminal-deleted peptide after obtaining the C-terminal-deleted peptide and before obtaining the C-terminal-deleted peptide-derived peptide fragments (see abstract).

In regard to Claim 14, Miyazaki teaches obtaining the C-terminal-deleted peptide while the peptide is retained in gel.

In regard to Claims15 and 16, Miyazaki teaches that acetylation, C-terminal amino acid deletion, hydration and trypsin digestion are all performed in gel (see abstract).

In regard to Claim 18, Miyazaki teaches isolating the peptide from the peptide mixture by gel electrophoresis and obtaining the C-terminal-deleted peptide is performed while the isolated peptide is retained in the gel (see abstract). Miyazaki dose not specific teach using polyacrylamide gel (PAGE gel) in his abstract. Since PAGE gel

is most commonly used gel for separating proteins and peptides, using PAGE gel is inherent part of Miyazaki's method or it is obvious to ordinary skill in the art.

In regard to Claim 19, Miyasaki teaches immersing the gel in a solution of acetic anhydride and formamide (see abstract). Formamide is a dipolar aprotic solvent.

In regard to Claims 22 and 23, Miyazaki teaches that the alkanoic anhydride is acetic anhydride (see abstract).

Claim Rejections - 35 USC § 103

12. The text of those sections of Title 35, U.S. Code can be found above.

13. **Claims 5 and 6** are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsugita.

In regard to Claim 5, the first three steps of the claim are disclosed by Tsugita as depicted in paragraph 8 of the present Office action. Tsugita does not specifically teach cleaving C-terminal-deleted peptides at predetermined position after obtaining C-terminal-deleted peptide. However, Tsuguta teaches that the routine measurement of protease-cleaved fragments have been used for identification, referred to as "peptide-mass fingerprinting" (see page 929, left col. 4th paragraph). Tsuguta further demonstrates cleaving at carboxyl side of aspartic peptide bond (Asp-C) and the amino side of the serine or threonine peptide bonds (Ser/Thr-N) before mass spectrometry analysis to improve the accuracy because of reduced peptide size (see page 931, left col. last paragraph; right col. 1st paragraph). The court has held that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (see *In re Burhans,* 154 F.2d 690, 69 USPQ 330 (CCPA 1946)). In that regard, Tsuguta teaches that cleaving peptide at predetermined position allows C-

terminal sequencing at multiple sites (see page 934, right col. first paragraph). Therefore, cleaving the peptide at predetermined positions before or after successive degradation of peptide is *prima facie* obvious in the absence of unexpected results.

In regard to Claim 6, modified Tsugita method would teach obtaining peptide-derived peptide fragments by cleaving peptide at predetermined positions (see page 931, left col. last paragraph; right col. 1st paragraph); and measuring the molecular weight of peptide-derived-peptide fragments, and C-terminal-deleted peptide-derived peptide fragments to determine the decrease in molecular weight of associated sequential degradation (see Table 3).

14. **Claims 7-13** are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsugita in view of Covey et al. (US Patent No. 5,952,653) (Covey).

In regard to Claims 7-9, Tsugita uses acetic anhydride to acetylate N-terminus amino group and to form oxazolone at the C-terminal carboxyl group (see page 930, left col. 3rd paragraph). It is known in the art that the amino group of lysine is susceptible to acetylation and acetic anhydride acetylates amino group of lysine (N-acylation) and hydroxyl group of serine and threonine (O-acylation). Acetylated residues are protected from the cleavage of trypsin. Tsugita is silent on cleaving the peptide by trypsin.

Covey discloses a method of using trypsin to cleave a protein and analyzing the result by mass spectrometry (see abstract). Covey teaches that arginine is basic and picks up a positive charge proton in a solution. Thus, the tryptic fragments will be doubly positively charged because of the inclusion of arginine at C-terminal and an amino terminus in each fragment (see Col. 2, lines 63-66). Covey further teaches that the charge difference makes the C-terminus fragment stands out from the other tryptic

fragments, because the C-terminus fragment has no arginine at C-terminus and therefore, will not have two positive charges (see col. 5, lines 58-62). In other words, in the mass spectra, the C-terminus fragment shows stronger intensity in anionic species, and all the other tryptic fragments show stronger intensity in cationic species.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to use trypsin cleavage and mass spectra analysis method as taught by Covey before mass spectrometry analysis of Tsugita with reasonable expectation, that trypsin cleavage would therefore increase the accuracy of the mass spectrometry measurement, because the trypsin cleavage reduces the size of peptide for mass spectrometry analysis, and in the mass spectra, the C-terminal peptide fragments obtained by successive release of the C-terminal amino acids would stand out by showing stronger intensity in anionic species, while all the other tryptic fragments would show stronger intensity in cationic species.

In regard to Claim 10, the hydrolysis as taught by Tsugita would remove acetyl group from O-acylation and therefore, would deprotect the side chain of serine and threonine from trypsin. The timing of the hydrolysis in the modified Tsugita method would have been after obtaining the C-terminal-deleted peptide and before obtaining the C-terminal-deleted peptide-derived peptide fragments (see page 930, right col. last 5 lines).

In regard to Claim 11, as has been discussed in regard to Claim 7-9, the combined teaching of Tsugita and Covey teaches that in the mass spectra, C-terminal-deleted peptide-derived peptide fragments (the C-terminus fragments) shows stronger

intensity in anionic species, and all the other tryptic fragments show stronger intensity in cationic species. Therefore, C-terminal-deleted peptide-derived peptide fragments can be identified by comparing the mass spectrometry results based on cationic species with the ones based on anionic species.

In regard to Claims 12 and 13, the modified method of Tsugita teaches allowing a water solution containing DMAE to act on the C-terminal-deleted peptide after obtaining the C-terminal-deleted peptide and before obtaining the C-terminal-deleted peptide-derived peptide fragments (see page 930, right col. last 5 lines).

15. **Claim 11** is rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazaki in view of Covey.

In regard to Claim 11, Miyazaki teaches measuring the molecular weight of C-terminal-deleted peptide-derived peptide fragments by MALDI-TOF MS (see abstract). Miyazaki also teaches cleaving C-terminal-deleted peptide with trypsin. Miyazaki does not specifically teach the method of comparing the mass spectra of cationic species with the mass spectra of anionic species in his abstract. Covey discloses a method of using trypsin to cleave a protein and analyzing the result by mass spectrometry (see abstract). Covey teaches that arginine is basic and picks up a positive charge proton in a solution. Thus, the tryptic fragments will be doubly positively charged because of the inclusion of arginine at C-terminal and an amino terminus in each fragment (see Col. 2, lines 63-66). Covey further teaches that the charge difference makes the C-terminus fragment stands out from the other tryptic fragments, because the C-terminus fragment has no arginine at C-terminus and therefore, will not have two positive charges (see col. 5, lines 58-62). In other words, in the mass spectra, the C-terminus fragment shows stronger intensity in

anionic species, and all the other tryptic fragments show stronger intensity in cationic species. At the time of the invention, it would have been obvious to one of ordinary skill in the art to compare the mass spectra of cationic species with the mass spectra of anionic species in order to distinguish the C-terminus fragment from other tryptic fragments as taught by Covey.

16. **Claims 14-16, 18 and 19** are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsugita in view of Vogt et al. (Polymer Bulletin, 1996) (Vogt).

In regard to Claims 14-16, Tsugita teaches separating peptide from the peptide mixture by SDS-gel electrophoresis (see page 929, 2nd paragraph). Tsugita does not teach obtaining the C-terminal-deleted peptide while the peptide is retained on gel. Tsugita teaches that the pretreatment and cleavage sub-step of the procedure needs to be carried out in the absence of water (page 931, right col. 2nd paragraph, last 2 lines; page 930, 3rd paragraph). Therefore, the target protein has to be extracted from the gel and then dried to remove water or electroblotted to an Immobilon-CD membrane. The consequence of extracting peptide from a gel after separation is that some peptide will be lost during the process (it is true to any peptide or protein processing). Therefore, sequencing the peptide while it is bound to a gel would avoid the loss of peptide during extraction. Vogt teaches a new non-aqueous swelling system; specifically Vogt teaches that carboxymethyl cellulose (CMC) gel treated with a dipolar aprotic solvent like N,N-dimethylacetamide with p-toluenesulfonic acid yields a high reactive gel-suspension of the polymer (see abstract). This dipolar aprotic solvent can remove water from the swollen gel in one step (see page 550, 3rd paragraph), thus allowing a direct esterification of the hydroxyl group of CMC (see abstract). At the time of the invention, it

would have been obvious to one of ordinary skill in the art to use polar aprotic solvent to remove water and use dipolar aprotic solvent to remove water from the gel carrier bound with the target protein, as taught by Vogt with reasonable expectation that this would allow Tsugita's procedure to be carried out while the target peptide is kept on the gel carrier. That way, the loss of peptide during extraction from a gel can be avoided.

In regard to Claim 18, Tsugita teaches isolating peptide from the peptide containing mixture by polyacrylamide gel (SDS-PAGE gel) electrophoresis before obtaining the C-terminal–deleted peptides (see page 929, right col. 2nd paragraph). As has been discussed in regard to Claim 16, the combined method of Tsugita and Vogt teaches obtaining the C-terminal-deleted peptide while the isolated peptide is retained in PAGE gel.

In regard to Claim 19, as has been discuss in regard to Claim 16, the combined method of Tsugita and Vogt teach obtaining the C-terminal-deleted peptide includes immersing the gel in a solution of an alkanoic anhydride in a dipolar aprotic solvent.

17. **Claim 17** is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsugita in view of Vogt as applied to Claims 14-16, 18 and 19 above, and further in view of Wirth et al. (US Patent No. 3,836,433) (Wirth).

In regard to Claim 17, Tsugita does not teach cross linking peptide before successively cleaving C-terminal peptides to fix the peptide on the gel. However, it would have been obvious to a person of an ordinary skill in the art to fix the peptide on the gel to reduce the loss of the peptide from the gel. Also, Wirth discloses using aldehydes e.g. glutaraldehyde to fix nitrogenous materials, e.g. amino acids, proteins, enzymes to insoluble supports which form gels in aqueous media, e.g. polyacrylamide

(see abstract). At the time of the invention, it would have been obvious to one of ordinary skill the art to modify Tsugita-Vogt's method by fixing peptide on the gel with glutaraldehyde as taught by Wirth in order to reduce the loss of peptide from the gel.

18. **Claim 17** is rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazaki in view of Wirth.

In regard to Claim 17, Miyazaki does not teach cross linking peptide before successively cleave C-terminal peptides to fix the peptide on the gel. However, it would have been obvious to a person of an ordinary skill in the art to fix the peptide on the gel to reduce the loss of the peptide from the gel. Also, Wirth discloses using aldehydes e.g. glutaraldehyde to fix nitrogenous materials, e.g. amino acids, proteins, enzymes to insoluble supports which form gels in aqueous media, e.g. polyacrylamide (see abstract). At the time of the invention, it would have been obvious to one of ordinary skill the art to modify Tsugita-Vogt's method by fixing peptide on the gel with glutaraldehyde as taught by Wirth in order to reduce the loss of peptide from the gel.

19. **Claims 20-21** are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsugita in view of Zeldin et al. (US Patent No. 5,442,106) (Zeldin).

In regard to Claims 20 and 21, Tsugita teaches that obtaining C-terminal-deleted peptide is carried out in a system containing a basic nitrogen-containing compound (DMAE) (see page 930, right col. 3rd paragraph). Tsugita teaches that DMAE is used as a basic catalyst for hydrolyzing ester into carboxyl group (see page 930, right col. 3rd paragraph). Tsugita is silent on using nitrogen-containing aromatic ring compound as the basic catalyst for ester hydrolyzation. However, simple substitution of one known element for another to obtain predictable results is obvious according to recent

Supreme Court ruling. [see *KSR International Co. v. Teleflex Inc.,* 550 U.S. , 82 USPQ2d 1385, 1395-97 (2007)]. In that regard, nitrogen containing compounds, e.g. DMAE and pyridine are known basic catalysts for ester hydrolysis. For example, Zeldin disclose using pyridine derivative compound as catalyst for hydrolyzing esters (see abstract). At the time of the invention, it would have been obvious to one of ordinary skill in the art to substitute DMAE utilized in Tsugita's method for pyridine derivative disclosed by e.g. Zeldin, because these are well known compounds for catalyzing ester hydrolyzing which lead to predictable results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT XU whose telephone number is (571)270-5560. The examiner can normally be reached on Mon-Thur 7:30am-5:00pm, Fri 7:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571)272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

10/1/2008

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

RX